The Underappreciated Role of Lifestyle and Nutrition in Cancer Prevention, Genesis, and Treatment

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Abstract: This article presents a review of the impact of nutrition and lifestyle on the most frequently occurring cancers, including blood, bone, brain, breast, gastric, lung, oral, pancreatic and skin cancers. Heart disease and cancer are the leading causes of morbidity and mortality and the first and second leading causes of death in the United States. Risk of death declined more steeply for heart disease than cancer, offsetting the increase in heart disease deaths, which partially offsets the increase in cancer deaths resulting from demographic changes over the past four decades. Lung cancer is by far the most common cause of cancer-related mortality worldwide in many countries. The incidence rates of lung, colorectal and prostate cancers will continue to rise in the future decades due to the rise of ageing population. Pancreatic cancer is an aggressive malignancy with a poor long-term survival and there has been only slight improvement in outcomes over the past 30 years. Some of the most common contributing factors to various cancers include: genetics, tobacco use, infections, obesity, poor diet, physical inactivity, environmental pollution and hazards, ionizing and ultra-violet radiation (UVR), sunlight, cancer causing substances, chronic inflammation and immunosuppression. This article summarizes recent and tangible cancer control measures which include early detection, weight control, Mediterranean type diet, phytochemicals such as flavonoids, regular physical activity, therapeutic agents, chemotherapy, nano-medicine, medicinal plants and education through mass media awareness.

Keywords: Prostate cancer, nano-particles, phytometabolites, solar UVR, cancer stem cells, mastectomy, prevention, diet.

INTRODUCTION

Cancer, a multifactorial disease, is defined as a serious and sometimes deadly disease categorized by the growth of abnormal cells that form tumors which may damage or destroy normal body tissue. It is ultimately the result of cells that uncontrollably grow and do not die. On the other hand, the normal cells in the body follow an orderly path of growth, division and death and such automated death is known as apoptosis. When this process breaks down, cancer begins to form. Cancer cells divide persistently, forming solid tumors or flooding the blood with abnormal cells. These tumors may be benign (not cancerous), pre-malignant (pre-cancerous) or malignant (cancerous). These cells can also spread to other parts of the body, a process known as metastasis. As cancerous tumors grow, some cancer cells break off and travel to distant places in the body through the blood or the lymph system and form new tumors far from the original tumor. Our growing understanding of cancer cell biology and tumor progression is gradually leading towards rational, tailored medical treatments designed to terminate cancer cells by manipulating the unique cellular pathways that distinguish them from normal healthy counterparts [1].

The precise origin of cancer has been a source of debate due to the scarcity of historical evidence [2]. The earliest reference to cancer is credited to the great Egyptian physician Imhotep, who lived around 2600 B.C. Imhotep's writings describe a condition characterized by a "swollen mass in the breast" that was unaffected to any known therapies. The most ancient texts had little to offer on the disorder, and functionally accurate descriptions of malignant tumors didn't appear until the late 18th century. Cancer is a relative newcomer in the historical record since it most commonly afflicts those 65 and older, and for a long time, few people lived long enough for cancer to become a concern [2]. The earliest identifiable case of malignant neoplastic disease from an early human ancestor is dated to 1.8-1.6 million years old [3].

Cancer is a most common cause of death in China and the United States. Some of the treatments for cancer include surgery, radiation, chemotherapy, targeted therapy and immunotherapy, with chemotherapy one of the most important treatment

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modalities [4]. Chemoprevention using dietary phytochemicals such as triterpenoids, isothiocyanates, and curcumin offer a promising alternative strategy in cancer prevention [5]. The updated meta-analysis confirms an important inverse association between adherence to a Mediterranean diet and cancer mortality and especially colorectal cancer [6]. Ginsenosides may also suppress cancer cell proliferation through anti-oxidation on tumor initiation and induced apoptosis. These various effects rather than a single effect may play a crucial role in evolving ginsenosides as an effective anticancer drug [7].

An excellent summary of numerous kinds of cancers as reported in the United States in 2107 listed as new cases have been methodically described [8]. The most newly available preventive methods include the use of Newfoundland seaweed extract which has been shown in-vivo tests to stop the growth of human cancer cells injected into mice [9]. This article will include in simplified form the most commonly occurring cancers, their genesis and preventive control measures.

KIND OF CANCERS AND POSSIBLE CAUSES OF THEIR INCIDENCE AND PREVENTIVE MEASURES

Heart disease and cancer are the first and second leading causes of death in the United States [10]. The danger of death declined more sharply for heart disease than cancer, offsetting the increase in heart disease deaths, which partially compensates the increase in cancer deaths resulting from demographic changes over the past 4 decades. If current trends continue, cancer will become the chief cause of death by 2020 [10].

Each cell holds a copy of DNA; the genetic blueprints that instruct them how, what, and where to grow, as well as how to replicate them. When the genetic data in a cell is damaged, the cell can start replicating nonstop, developing a growth. These growths can remain benign without metastasizing to other parts of the body, or become malignant; even benign growths can become malignant. Usually, our bodies will destroy these cells on their own, but at times they can replicate beyond the body's control. When the body can no longer stop these cells from growing, they become a cancerous tumor. This section will limit discussion to the most common cancers.

a. Blood Cancer

There are three main types of blood cancers: 1. Leukemia**,** found in blood and bone marrow, is caused by the rapid production of abnormal white blood cells (WBC), II. Lymphoma affects the lymphatic system, which removes excess fluids from the body and produces immune cells, and III. Myeloma is a cancer of the plasma cells.

Hematologic malignancies, account for about 10% of all deaths for cancer [11]. Most blood cancers occur in the elderly. This fact combined with an aging population in many countries makes rigorous assessment for ill-health increasingly important for hematologic oncologists [12]. Hypoxia is an essential micro environmental factor of bone marrow pathophysiology. Current data from molecular and clinical studies indicate that hematopoiesis and leukemogenesis are dependent upon hypoxia-inducible factors (HIFs), a family of vital transcriptional activators mediating the metazoan hypoxic response. In blood cancers, the synergism between HIF overexpression and stabilization within the hypoxic bone marrow microenvironment stimulates disease development, therapy resistance, and decline [13].

Cancer stem cells (CSC), also known as tumor-initiating cells (TICs), are characterized by high self-renewal and multi-lineage differentiation capacities. These cells are thought to play crucial roles in the initiation, development and metastasis of many cancer types. Leukemia are thought to be initiated and preserved by a specific sub-type of CSC, the leukemia stem cell (LSC) [14]. Acute myeloid leukemia (AML) is a cancer of the myeloid lineage of blood cells. Although major progress has been made in treating many cancer types during recent years, AML remains a deadly disease with survival rate lagging behind other blood cancers [15]. Cancer heterogeneity is a noteworthy factor in response to treatment and escape leading to relapse. Within an individual cancer, especially blood cancers, there occur multiple subclones as well as discrete clonal increases unrelated to the clinically detected, leading clone [16].

Currently, monoclonal antibodies (mAbs) are prevalent and essential tool for biomedical science. In the hematological cancer field, since rituximab became the first mAb approved by the Food and Drug Administration for the treatment of B-cell malignancies, a number of effective mAbs targeting lineage-specific antigens have been effectively developed [17**].** Therapeutic targeting of CSC using drugs that disturb activated developing pathways may also represent an attractive strategy that is possibly relevant to many types of malignancy, especially blood cancers, where

the evidence for LSC is well established [18]**.** Many PI3K pathway-targeted therapies have been tested in oncology trials, resulting in regulating approval of one isoform-selective inhibitor (idelalisib) for treatment of certain blood cancers and a diversity of other agents at different stages of development [19].

New therapeutics target molecules such as proteins and cellular mediators and the subject of present drug development, which may suggest new avenues to attack multiple myeloma, a destructive blood cancer. [20]. Omega-3 polyunsaturated fatty acids (PUFAs) have well recognized anti-cancer properties. For example, eicosapentaenoic acid and docosahexanoic acid PUFAs have a high protection profile and can induce apoptosis and inhibit growth of cancer cells both *in vitro* and *in vivo*, following a partly selective manner. They also increase the efficiency of chemotherapeutic agents by increasing the sensitivity of different cell lines to specific anti-neoplastic drugs [21]. Novel and upcoming strategies for immune checkpoint barrier drug development in hematologic malignancies using advanced combinations to control immunologic targets show significant promise as a way to expand the number of patients with blood cancers who could benefit from immunotherapy [22]. Among the large number of target antigens, CD19 is the best target for chimeric immunoreceptors (CAR) T cell therapy for blood cancer, but CAR-engineered T cell immunotherapy does not yet work in solid cancer. The cancer-testis gene, NY-ESO-1 is one of the best targets for T cell receptor-based immunotherapy in solid cancer [23].

b. Bone Cancer

Osteosarcoma is the most common cancer that occurs in young adults and adolescents. Drug resistance is the main cause leading to therapeutic failure. Current research associates microRNA with drug resistance in osteosarcoma cells, raising the awareness that targeting microRNAs may help in chemotherapy success [24]. One of the leading causes of death among patients with malignancies is characterized by bone cancer [25]. For the assessment and monitoring of bone cancer, the expression of miRNAs can be effectively used due to increased specificity. Using miRNAs as gene therapy can be also considered a therapeutic method of the future, mainly due to careful and targeted response of the body [25]. Despite an incidence of three cases of osteosarcoma per million annually, it accounts for an excessive amount of morbidity and mortality. While the use of chemotherapy (cisplatin, doxorubicin, and methotrexate) in the last century initially resulted in fringe improvement in survival over surgery alone, survival has not enhanced further in the past four decades [26]. Autopsy studies have shown that 70% of patients with breast and prostate carcinoma develop skeletal metastases. The most commonly involved bone sites are those with persistent red marrow, such as the vertebrae, proximal femur, ribs, sternum, pelvis and skull [27].

A common cause of morbidity in patients with primary bone cancer and bone metastases is due to skeletal complications. Thus, offering the prospect of identifying selective cannabinoid receptor type 2 encoded by the Cnr2 ligands, as novel, alternative to cannabis herbal extracts is for the treatment of progressive cancer patients [28]. Current therapy for metastatic bone cancers often produces highly morbid side effects. Osteonecrosis of the jaw (ONJ) is a rare treatment related side effect that was first described in 2002 through a case report in metastatic bone cancer patient treated with bisphosphonates treatment [29].

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma. Patients with MCL generally present with wide ranging lymphadenopathy and extranodal association. In a rare case the patient was diagnosed with primary bone MCLs and chemotherapy was administered. During the 2-month follow-up, the patient remained in a good clinical condition [30]. Osteolytic cancer in the bone leads to release of transforming growth factor beta (TGFβ) from the bone via osteoclast-mediated bone destruction. A new role has been identified for bone-derived TGFβ as a cause of skeletal muscle feebleness in the setting of osteolytic cancer in the bone [31].

Despite the significant occurrence of osteoarthritis, osteoporosis, non-union bone defects, bone cancer, and myeloma-related bone disease, their effective treatments remain a challenge [32]. The success of dynamic immunotherapies in the prevention of many infectious diseases over the course of over 200 years has lead scientists to wonder if the same ethics could be applied to cancer. This highlights the importance of taking into consideration the location of vaccine-derived heat shock proteins /tumor-antigen complexes when designing vigorous immunotherapeutic approaches [33]. There appears to be evidence that melatonin lessens cancer at the beginning, progression and metastasis phases, suggesting the benefits of using melatonin as a co-treatment with predictable cancer

therapies would far surpass progress in the wellbeing of patients [34].

c. Brain Cancer

About 238,000 new cases of brain and other central nervous system tumors are diagnosed each year around the world [35]. Glioblastoma multiform (GBM) is the utmost common and first leading cause of death in primary human brain cancers. In spite of continuous advancements in medicine, the median survival time of patients is unfavorable irrespective of radiotherapy, chemotherapy, or surgery. This poor conclusion is referred to the CSC concept [36]. Nano-particles offer the advantages upon numerous concerns, i.e., finding, capability to target therapeutic agents to the tumor sites and the ability of getting across the blood-brain barrier (BBB). Thus the application of nano-particles may lead to breakthrough in brain cancer management [35]. Glioblastoma multiform is a severe malignant brain cancer with poor overall endurance. Conventional intervention remains gloomy to prevent recurrence and deterioration of GBM cell [37]. It displays noteworthy inter-and intratumoral heterogeneity, and to control the GBM type of tumor, a tailored approach is required [38]. Seizures are one of the most common appearances of glioblastoma. The use of anti-epileptic drugs (AEDs) in glioblastoma patients suffering from seizures is well accepted. However, the role of long-term AEDs use in patients with glioblastoma without a history of seizures is contentious [39].

Gliomas are overwhelming brain cancers that have poor predictive outcomes for their patients. Short overall patient survival is due to a lack of robust, efficient treatment options. Next-generation therapy which emphasizes on infiltrative tumor phenotypes and disruption of the vascular and perivascular microenvironments harboring residual disease cells offers confidence for the restricted control of malignant gliomas [40]. Gliomas and leukemia remain highly intractable to treatment, thus stressing the need for new and improved therapeutic strategies [41].

Boron neutron capture therapy (BNCT) is likely a targeted chemoradiotherapeutic technique for the management of invasive brain tumors, such as GBM. A criterion for effective BNCT is the selective targeting of tumor cells with 10B-rich therapeutic moieties. The progress of carborane derivatives with high cancer-cell targeting specificity is the key to these materials fulfilling their promise as the clinical BNCT agents of the future [42]. Fish intake, rich in ω-3 polyunsaturated fatty acids, has been found to be associated with lower risk of several types of cancers, and beneficial for the development of brain [43]. Whilst chemotherapeutic agents show promising results in the amelioration of cancerous tumors, patients often experience cognitive disturbances associated with chemotherapy long after treatment has ceased. Chemotherapy induced white matter damage highlights the importance of implementing behavioral and pharmacological strategies to prevent or reverse such acute toxicity in the brain [44].

Brain cancer has no therapeutics available to fight, predominately due to the BBB preventing treatments from maintaining therapeutic levels within the brain. Lately, nano-particle technology has entered the forefront of cancer therapy due to its ability to deliver therapeutic effects while possibly passing physiological barriers [45]. Antibodies have also been shown to be a potent therapeutic tool. However, their use for targeting brain diseases, including neurodegenerative diseases and brain cancers, has been restricted, chiefly because the BBB makes brain tissue hard to access by conventional antibody-targeting approaches. Following the success in treatment of leukemia and lymphomas, the adoptive T-cell therapies, especially the chimeric antigen receptor-T cells (CAR-Ts), are making their way into glioma treatment as another type of cell-based therapy using the antibody to bind to the precise target(s) [46]. Increasing evidence indicates that the adult neurogenic function of the ventricular-subventricular zone (V-SVZ), beyond serving as a potential site of origin, affects the outcome of malignant brain cancers [47]. Transmembrane protein 88 (TMEM88) was expressed at considerably higher levels in BC cell line than in normal breast cell line with co-localized with Dishevelled in the cytoplasm of BC cell line. Wnt signaling pathway is activated during cancer development. TMEM88 has an influence on cancer by preventing canonical Wnt signaling [48].

d. Breast Cancer

Breast malignancies are the most common cause of cancer-related deaths for women in developed countries. Development of human epidermal growth factor 2 (HER2)-targeting drugs has been considered a breakthrough in anti-cancer tactics and alluded to the potential of targeting growth factors in breast cancer (BC) therapeutics [49]. Breast cancer contributes considerably as the primary cause of female cancer related deaths [50]. Tumor-associated macrophages are capable of prompting angiogenesis, remodeling the

tumor extracellular matrix to aid invasion, modeling BC cells to scape host immune system and recruiting immunosuppressive leukocytes to the tumor microenvironment. Tumor-associated macrophages are a striking target for therapeutic intervention by targeting various aspects of their function [50]. Neutrophil gelatinase-associated lipocalin determination in plasma and urine could be useful in the prognosis of BC and colorectal cancer, but its predictive accuracy remains uncertain for other human tumors [51]. Metformin is also found to be related with the danger for development of several human solid cancer types such as colorectal, breast and pancreas cancer in the diabetic patients [52].

Obesity is particularly recognized as a risk factor for developing BC in postmenopausal women [53]. Adipose tissue in the breast under obese conditions prompts inflammation by increasing macrophage infiltration and pro-inflammatory cytokines that in turn up-regulates genes and signaling pathways, causing increased inflammation, cell proliferation and tumor growth in the breast. Due to their powerful anti-inflammatory effects, n-3 polyunsaturated fatty acids are a promising and safe dietary intervention in reducing BC risk [53]. Receptor activator of nuclear factor kappa-B (RANK) treatment may form a defensive strategy in patients at high risk for malignancies of the breast [54]. Obesity is causally related to cancer at 13 anatomic sites (esophagus: adenocarcinoma; gastric cardia; colon and rectum; liver; gallbladder; pancreas; breast: postmenopausal; uterine endometrial; ovary; kidney: renal cell; meningioma; thyroid; and multiple myeloma) [55]. In the context of life style risk factors, obesity, alcohol, chronic estrogen signaling and smoking have distinct BC precipitating and facilitating effects that may act alone or in combination [56]. Online tools are valuable in guiding adjuvant treatment, especially in resource constrained countries. However, in the era of personalized therapy, molecular profiling appears to be superior in predicting clinical result and guiding therapy [57].

Breast cancer therapy is the most common cause of secondary lymphedema in the developed world. Treatment includes nonsurgical and surgical strategies. Surgical options effectively decrease edema and improve quality of life. However, further research is necessary to best institute management of lymphedema [58]. Prophylactic or 'risk-reducing' mastectomy refers to the process of completely removing a healthy breast in order to reduce the risk of developing BC. For women who are not high-risk gene carriers for BC but have other factors, such as strong family history, tumor characteristics that may increase their risk, more proof is needed as the benefit of contralateral prophylactic mastectomy and all decisions to undertake it should occur through a multidisciplinary team approach [59]. Hypo fractionated whole blood irradiation (WBI) can be completed in 3 to 4 weeks and, based on long-term randomized data, is the preferred standard of care in select patients. Accelerated partial-breast irradiation can be delivered using even shorter treatment regimens. Although the available data on such irradiation is more limited, however it is an effective alternative to WBI in select patients [60].

Phosphoinositide 3-kinase (PI3K) inhibitor decreases the risk of progression in unselected advanced BC patients and chiefly in patients with an activated PI3K pathway detected on cell-free tumor (ct)-DNA analysis. However, their significant dose-limiting toxicity is a limiting factor [61]. The results of a meta-analysis showed that women who consumed red meat had a higher risk of BC. Further studies are required to investigate this association [62]. Human carcinoembryonic antigen (CEA) is the prototypic member of a family of highly related cell surface glycoproteins that includes carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) and others. Carcinoembryonic antigen-related cell adhesion molecule functions as a pan-inhibitor of cell differentiation and cell polarization, and it also causes distortion of tissue architecture [63]. Many common environmental chemicals are mammary gland carcinogens in animal studies, which activate relevant hormonal pathways, or enhance mammary gland susceptibility to carcinogenesis. New studies that targeted toxicologically relevant chemicals and captured biological hypotheses about genetic variants or windows of breast susceptibility added to evidence of links between environmental chemicals and BC [64]. Breast cancer remains the leading cause of cancer-related deaths in premenopausal women. The use of breast-specific liquid biopsies, such as nipple aspirate fluid (NAF), a natural secretion produced by breast epithelial cells, can be collected non-invasively for biomarker profiling [65].

In addition to a sedentary life style, low physical activity, and low serum 25(OH)D levels among women diagnosed with BC, an association has been reported between reproductive and dietary factors [66]. This finding showed a significant association of reproductive and dietary factors in addition to being less active than low serum 25(OH)D levels in women diagnosed with

BC [66]. This finding showed a significant association of reproductive and dietary factors in addition to being less active and low serum 25(OH)D levels in women diagnosed with BC [66]. There is some evidence that curcumin may have antitumor activity in BC. Lipid-based nano-micelles is another method to improve curcumin absorption via the GI tract, while polymer-based nano-formulations, e.g., poly D, L-lactic-co-glycolic allows the release of curcumin at a sustained level [67].

Breast conservation therapy was recognized as the favorite modality of surgical treatment for early stage BC in the early 1990's. There is a pressing need to formulate strategies to effectively inform both patients and practitioners about current data, in the hope of reversing rising mastectomy rates to optimize survival outcomes [68]. Based on limited data, Proton beam radiotherapy (PBT) provides favorable quality of life and patient reported outcome (QOL/PRO) profiles for select brain, head/neck, lung, and pediatric cancers; measures for prostate and BC were more modest. These findings have implications for cost-effective cancer care and cautiously designed QOL evaluation in ongoing trials [69].

Radiation therapy (RT) has been effectively used in the treatment of BC for over a century. Immunotherapy is showing promise in treatment of various cancers, including BC, and can be an ideal complement to RT in stimulating a systemic immune response to reject the tumor cells [70]. There is a need for tailored physical activity plans to be developed to suit the individual and their situations [71]. Acupuncture is effective for cancer-related fatigue (CRF) management and should be recommended as a beneficial alternative therapy for CRF patients, particularly for BC patients and those currently undergoing anti-cancer treatment [72].

e. Gastric Cancer

The medical outcome of gastric cancer (GC) patients is still not encouraging with a low rate of 5 year survival. Often the disease is diagnosed at advanced stages and this obviously negatively affects patients' outcomes [73]. Chronic Helicobacter pylori *(H. pylori*) infection is considered the main cause of GC [74]. Gastric cancer stem cells have been identified as the cell compartment able of self-renewal and differentiation responsible for tumor continuous growth [74]. The gastrointestinal microbiome is a complex ecosystem that institutes a symbiotic, mutually beneficial relation with the host, being rather stable in health, but affected by age, drugs, diet, alcohol and smoking. Changes in the stomach and *H. pylori*-related disorders are seriously affected by alcohol consumption and smoking [75].

The success of targeted therapy and immunotherapy in BC and melanoma, respectively, has not been duplicated in GC, but trastuzumab and ramucirumab have confirmed efficacy in select populations [76]. Its occurrence remains highest among Asian/Pacific Islanders likely due to the gene-environment interaction [77]. Epstein-Barr virus-associated gastric carcinoma (EBV-aGC) is a recently recognized disease entity defined by the presence of EBV in gastric carcinoma cells. Epstein-Barr virus infection causes major epigenetic alterations in the EBV genome and its cellular host genome, proposing that EBV acts as a direct epigenetic driver for EBV-aGC [78].

Melatonin with known powerful inhibitory effects on cancer cells is one of the major candidates which can be recruited herein. It is a pleiotropic anti-cancer molecule that affects malignant cells via multiple mechanisms [79]. The steady decline in incidence in East Asia will continue as primary and secondary prevention strategies are employed. Eventually, global *H. pylori* extinction will be needed to largely eliminate GC [80, 81]. *H. pylori* infects the stomach and can lead to, among other disorders, the development of GC. The failure of the host to clear the infection results in a prolonged inflammatory state with continued oxidative stress within the tissue [82]. Recognizing and confirming diagnostic, predictive, and therapeutic biomarkers will have a huge impact on patient's outcomes as they will allow early detection of tumors and also guide the choice of a targeted therapy based on specific molecular features of the cancer [73].

For patients with extensive carcinomatosis, the completeness of cytoreductive surgery is a critical prognostic factor for survival [83]. Cytoreductive surgery and hyper thermic intraperitoneal chemotherapy (HIPEC) are indeed promising treatment options for GC with peritoneal carcinomatosis and warrants a large randomized clinical trial [84]. Sentinel node navigation surgery can lead to actual organ-preserving surgery and plays a key role in improving the quality of life of patients with early GC in the future [85]. Since Wnt signalling is a driver of gastric tumorigenesis, Wnt pathway in GC patients strongly proposes that Wnt-targeted therapies could offer therapeutic benefits for GC patients [86]. Medicinal

plant products such as curcumin, quercetin, and allicin seem to be good candidates to control GC through their pro-apoptotic, anti-proliferative, and anti-helicobacter activities [87]. A number of observational studies and meta-analyses have shown that long-term statin use considerably decreases the GI cancer incidence [88].

The development of upper GI cancers, especially in low-resource settings, is affected by the environmental factor of biomass smoke exposure [89]. Several studies have been conducted to determine the correlation between tumor necrosis factor-α (TNF-α) 238 G/A polymorphisms and gastric carcinoma risk but the results are conflicting. In a group study, TNF-α 238 G/A polymorphism was statistically associated with the increased risk of gastric carcinoma, especially in Caucasians [90]. Given the striking tumor regression results obtained with gastric vagotomy in GC models, and the effects of β-adrenergic blockade in pancreatic tumor models, it may be feasible to improve cancer outcomes with therapeutics targeted to the nervous system [91]. Also, there is some evidence for dietary whole grain intake to be useful in the prevention of certain diseases such as GC. The possible benefits of these results suggest that the consumption of 2 to 3 servings per day (~45 g) of whole grains may be a reasonable public health goal [92]. Systemic chemotherapy prolongs survival, improves symptom control, and helps maintain a better quality of life with metastatic GC patients [93].

Malignancy is a major determinant of sarcopenia, characterized by progressive and generalized loss of skeletal muscle mass and strength, and GC is among the most common causes of this phenomenon [94]. Gastric cancer requires multimodal treatment and surgery is the most effective treatment modality. Minimally invasive surgery has gained wide popularity and indications for minimally invasive procedures have been increasing due to growing experience and improving technology [95]. Location of the primary GC in the upper third of the stomach, particularly at the GEJ/cardia, should be acknowledged as an important predictive factor [96]. Hereditary GC a rare disease is predominantly caused by germline mutations in CDH1 [97]. In China, higher levels of Prostaglandin E2 and, the urinary metabolite PGE-M, may indicate an increased risk of GC independent of the risk conferred by *H. pylori* infection status, particularly for cancers diagnosed within 10 years of sample collection [98].

Exosomes, vesicles of endocytic origin ranging from 30 to 100 nm in size and composed of a lipid bilayer containing DNA, mRNA, miRNA, circular RNA and multiple proteins, play a vital role in GC carcinogenesis and metastasis [99]. Overall, cluster-of-differentiation (CD) 44 (cell surface receptor) variable isoforms (CD44v), in particular CD44v9, are believed to mark the GC cells that contribute to increased reistance for chemotherapy-or radiation-induced cell death [100].

f. Lung Cancer

Most centers optimize lung cancer (LC) patients with chest physiotherapy and smoking cessation preoperatively. Minimally invasive techniques are gaining popularity with video-assisted thoracoscopic surgery predominating over robotic surgery [101]. In Australia, LC was the most common cause of cancer death in both males and females. [102]. Lung tumors are often associated with a poor prognosis although different schedules and treatment modalities have been extensively tested in clinical practice. Technological improvements of clinical linear accelerators allow combining high dose-rate and a more conformal dose delivery with accurate imaging modalities pre- and during therapy [103]. Accumulating evidence suggests that inhibition of receptor activator of nuclear factor kappa-B ligand (RANKL) does not only induce an increase in bone mass and strength, but also has anti-tumor effects. In addition, RANKL treatment may form a preventative strategy in patients at high risk for malignancies of the breast [54]. Ginsenoside Rk1, a unique component created by processing the ginseng plant, also has a significant anti-tumor effect on several cancers, including LC against *in vitro* cell lines [104].

Epidermal growth factor receptor (EGFR) is the most common driver gene involved in non-small cell lung cancer (NSCLC) growth, being found in approximately 10 - 15% of Caucasian and 40% of Asian patients [105]. Latest studies have shown advances in survival following surgical resection with chemotherapy in patients with early-stage SCLC, specifically in those with stage 1 disease [106]. Lung cancer includes several disease groups with NSCLC accounting for ~ 85% of cases and lung adenocarcinoma being its most common histological subtype [107]. Despite advances in targeted treatments, LC remains a common deadly malignancy in typical late presentation [108]. Positron emission tomography (PET) scanning plays key roles in designing the management of patients with LC who are candidates for curative-intent treatment with radiotherapy and has contributed to improvements in survival. 18F-fluorodeoxyglucose-PET is the most

important modality for staging, patient selection, and radiotherapy target volume definition in patients with unresectable NSCLC [109].

Lung cancer patients diagnosed at Stage 1 are commonly curable and have a 5-year survival rate of 50–80% [110]. Immunotherapy is a promising treatment model that is gaining acceptance in managing several cancers, including LC [111]. Pulmonary tuberculosis infects one-third of world's population and is responsible for the high mortality and morbidity in developing countries. Clinical history and computed tomographic (CT) findings on a hybrid PET/CT are as important as findings on a PET in the diagnosis of LC [112]. It is a worldwide health issue that is overwhelmingly caused by smoking; however, a substantial minority (~25%) of patients with NSCLC has never smoked. In these patients, activating mutations of the EGFR are more likely, which render their tumors susceptible for a limited period to treatment with EGFR tyrosine kinase inhibitors and confer a better prognosis than EGFR wild-type NSCLC [113].

Oxidation stress and external exposures such as altered oxygen tension or air pollution contribute to the development of diseases such as chronic obstructive pulmonary disease (COPD), asthma and LC [114]. Aberrant expression and dysregulation of jumonji domain-containing protein 6 (JMJD6) are implicated in various other processes including LC [115]. The use of probiotics show better survival rates for LC with an augmented expression of tumor suppression genes. However, the expression of two oncogenes studied decreased but increased cytotoxic effects were observed in LC cells [116].

g. Oral Cancer

More than 90% of oral cancers occurring in the mouth, lip, and tongue are oral squamous cell carcinoma (SCC). Head and neck SCC is the sixth most common cancer worldwide [117]. Oral SCC located in the mouth, tongue or oropharynx is a noteworthy health problem and the most common malignant neoplasm of the oral cavity, usually affecting individuals over 50 years of age [118]. Brush biopsy or body fluid samples may be superior to surgical samples in allowing miRNA-based diagnosis and prognosis of oral SCC features a speedy method to obtain homogeneous tumor cells and/or RNA [119].

Delayed diagnosis and treatment of patients with oral cancer continues to be a leading cause of poor prognosis, which could be lessened by providing health information, particularly about risk factors, by improving the training and retraining of physicians and dentists and by improving access to the health system [120]. Oral mucositis is known to impede the quality of life in patients treated for oral cancer [121]. Topical vitamin E had performed better on oral mucositis than vitamin E systemic administration. Though the efficacy of topical treatment with vitamin A showed reduction in oral mucositis, it was evaluated in a very small sample which cannot be credited to a larger sitting [121]. The use of topical agents among patients with oral lesions may be a practical complement or even alternative to traditional surgery, radiation, or systemic chemotherapy, with the advantage of reducing systemic side effects and sparing important anatomic structures [122]. The use of topical 5-ALA-20% photosensitizers (PTS), associated to a LED light applied for 15 min with a 7-day interval between sessions emerged as the most frequently used photodynamic therapy practice, with appropriate results [123].

To provide more methods of cancer prevention, the role of bacterial and viral carcinogenesis in the oral cavity is of interest [124]. The general dental practitioners' role in the detection of early stage of oral cancers and other oral cavity malignant diseases is vital and it is of critical importance [125]. Early oral cancer is preferably treated by surgery and its complete removal is essential for loco regional control and disease-free survival [126]. Reprogramming energy metabolism is an emerging hallmark of cancer that is largely controlled by hypoxia-induced genes regulating angiogenesis, tumor vascularization, invasion, drug resistance and metastasis [127]. There are inconsistent results on the influence of coffee in oral and pharyngeal cancer risk; however inverse association between high coffee consumption and the risk of oral and pharyngeal cancers indicates that coffee may have a protective role against these cancers [128]. Green tea is known to defend healthy cells from malignant transformation and locally has the ability to induce apoptosis in oral cancer cells, thus green tea is beneficial in oral health [129]. Oral cancer treatment difficulties include oral mucositis, salivary gland hypofunction, odontogenic infections, pain, dermatitis, neurotoxicity, soft tissue fibrosis, trismus, osteoradionecrosis, and potential cancer reappearance [130]. Numerous environmental factors such as diet, alcohol use, stress, and environmental chemicals are known to cause epigenetic changes, leading to increased rates of cancers and other diseases [131].

h. Pancreatic Cancer

About 90% of pancreatic cancer is caused due to environmental risk factors and about 50% of these cases may be attributed to diet, which is largely modifiable [132]. Mortality remains alarmingly high for patients diagnosed with pancreatic ductal adenocarcinoma (PDA), with 93% give way to the disease within five years. The vast majority of PDA cases are driven by activating mutations in the proto-oncogene KRAS, which results in constitutive proliferation and survival signaling [133]. It is a deadly malignant disease associated with poor prognosis, in spite of recent medical advances. Pancreatic carcinogenesis is dependent on various events, e.g. gene alterations, environmental insults, and cell types [134].

Ginsenoside Rk1 produced by processing the ginseng plant has a significant anti-tumor effect on several cancers including pancreatic cancer demonstrated on *in vitro* cell lines [104]. Pancreatic cancer is a poor prognostic tumor and only about 20% of patients are eligible for surgical resection at the time of diagnosis [135]. The most frequent type PDA remains one of the most thought provoking problems for the biomedical and clinical fields, with low survival rates and poor therapy efficiency. Desmoplasia, which is abundant in PDA, can be blamed for much of the rationale behind poor drug performance, as it is the main source of the cytokines and chemokines that orchestrate speedy and silent tumor progression to allow tumor cells to be isolated into an extensive fibrotic reaction that results in ineffective drug delivery [136].

Family history is a significant risk factor for developing pancreatic cancer and this heredity risk can be secondary to familial cancer predisposition syndromes, hereditary pancreatitis, or familial pancreatic cancer. Certain high-risk individuals are recommended to undergo screening for pancreatic cancer with endoscopic ultrasound or MRI/magnetic resonance retrograde cholangiopancreatography because of the potential to categorize and curatively resect precursor lesions [137]. Rates of long-term survival after treatment of pancreatic cancer remain low, in part because most patients are still treated with primary resection. Preoperative therapy can be used to improve local control and treat the systemic nature of pancreatic cancer while also selecting for patients who benefit from a gloomy operation [138]. Factors, such as, health education, cancer screening, early detection and treatment should improve the hazard of this as well as other cancers.

i. Skin Cancer

In spite of various precautionary measures to avoid direct excessive ultraviolet radiation (UVR) exposure from the sun, the incidence of skin cancer and mortality related to it remains high. Chemo preventive strategy using naturally occurring compounds, such as resveratrol, is a promising approach to reduce the incidence of UVR-induced skin cancer and delay its advancement [139]. Annually, more skin cancer cases are diagnosed than the collective incidence of the colon, lung, breast, and prostate cancer. Ultra violet B radiation induces reactive oxygen species production in the skin which eventually leads to DNA damage and mutation. Ultra-flexible- and transethosomes-, nano-carriers, silica-, silver-, and polymer nano-particles, nano- capsule suspensions, micro- and nano-emulsion have been used so far to deliver the desired drug molecule for preventing the UVB-induced skin cancer [140]. Significant skin pigmentation disorders may cause not only cosmetic and psychological issues, but more importantly it increases the risk of skin cancer or photoaging. The molecular mechanisms of skin repigmentation following healing of burn injuries includes the differentiation of melanoblasts into melanocytes, the scattering and responses of melanocytes and melanocyte stem cells after burn injury, and the regulation of melanin production[141].

Although skin carcinogenesis is still not fully understood, several publications demonstrated that genetic and molecular alterations are involved in this process. In addition, plenty of non-melanoma skin cancer risk factors are now known, allowing for an effective prevention of non-melanoma skin cancer development [142]. Porocarcinoma a rare sort of skin cancer emerging from sweat glands is an aggressive skin cancer and surgery is the key modality of treatment [143]. Family doctors and clinicians should inform their patients about the increased risk of skin cancer associated with the use of calcium channel blockers and β-blockers and instruct them to perform periodic skin self-examination [144]. The Global Solar UV Index was established as an easy-to-understand measure of the amount of biologically-effective ambient solar UVR at different sites on the earth's surface. The UV Index as a risk communication tool continues to be useful for raising alertness and to support sun-protection behavior [145]. The UVR causes DNA damage in melanocytes by producing photolesions

such as cyclobutane pyrimidine dimers and 8-oxo-7-hydrodeoxyguanosine. As nicotinamide diminishes the incidence of actinic keratoses and non-melanoma skin cancers in high-risk persons and improves repair of DNA damage in melanocytes, it is a favorable agent for the chemoprevention of melanoma in high-risk inhabitants [146].

Melanoma and non-melanoma are the two major types of skin cancer observed in humans. Non-melanoma is further subdivided into basal cell carcinoma and squamous cell carcinoma. Numerous natural bioactive phytochemicals have been shown to exhibit epigenetic modulatory competence and act as chemo-preventive as well as therapeutic agents [147]. Melanoma is the deadliest form of skin cancer and its frequency is rising, creating a costly and significant clinical problem. Exposure to UVR, namely UVA (315-400 nm) and UVB (280-315 nm), is a major risk factor for melanoma progress. Cumulative UVR exposure from sunlight or tanning beds adds to UV-induced DNA damage, oxidative stress, and swelling in the skin. A number of factors, including hair color, skin type, genetic background, location, and history of tanning, determine the skin's response to UVR. In melanocytes, dysregulation of this UVR response can lead to melanoma [148]. For woman, a positive correlation was revealed between long-term night shift work and skin cancer [149].

Solar UVR radiation causes display of destructive cellular and molecular events that eventually lead to the development of skin cancer. Skin cancer chemoprevention using phytochemicals either as dietary supplements or by topical applications has gained substantial attention due to their low toxicity, obtainability, and anti-carcinogenic properties. Much current research is focused on prevention of skin cancer through sun blocks. These sun blocks use ingredients such as zinc oxide to reflect the UVR rays and therefore limit the body’s exposure to the harmful UVR. If properly applied sunblock can nearly completely block UVR from reaching the skin. Tea is a rich source of likely phytochemicals, known as polyphenols, in averting skin cancer [150]. The application of human microbiome in skin cancer research seems to be a promising field and may help yield novel skin cancer prevention and treatment options [151].

j. Other Miscellaneous Factors Related to Cancer

It has been advised that ERCC2 Asp312Asn polymorphism significantly increased cancer risk in Asian populations, but not in Caucasian populations [152]. In a Taiwan study conducted in Taiwan, smoking, alcohol use, and betel quid chewing were identified as the three major causes of head and neck cancers, these three social habits were commonly observed in males, resulting in an increasing morbidity rate of head and neck cancers in this population [131]. A meta-analysis endorses an important inverse relationship between adherence to a Mediterranean diet including higher intake of fruits, vegetables, and whole grains and cancer mortality and risk of several cancer types, especially colorectal cancer [6].

Osthol a natural coumarin isolated from Apiaceous plants has demonstrated several pharmacological effects, such as antineoplastic, anti-inflammatory and antioxidant properties. It exerts noteworthy anticancer properties by subduing various kinds of cancers cell growth and introduction of apoptosis. A large body of evidence shows that osthol regulates apoptosis, proliferation and invasion in different types of malignant cells which are mediated by multiple signal transduction cascades [153].

In an era of precision medicine, identification of hyper mutation and micro satellite instability will play a significant role directing surgical and chemotherapeutic treatment. Thus, in an era of precision medicine, identification of hyper mutation and micro satellite instability will play an important role directing surgical and chemotherapeutic treatment. There are several known causes of hyper mutation in tumors, such as UVR in melanoma, tobacco smoke in LC cancer, and excessive apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like activity in BC and GC [154]. Cancer in the elderly has become an increasingly common problem due to the prolonged life expectancy of the general population. Aging is related with progressive decrease in body's functional capacity and increased prevalence of chronic diseases. Consequently, cancer treatment could cause higher prevalence of serious side effects [155].

SUMMARY AND CONCLUSIONS

Advancement in reducing death rates and improving survival rates is restricted for several cancer types, which underlines the need for intensified efforts to discover new strategies for avoidance, early detection, and treatment and to apply proven preventive measures largely and justifiably [156]. Most cancers are characterized by defects in the systems that ensure strict control of the cell cycle in normal tissues. The

resulting excess tissue growth can be countered by drugs that halt cell division, and the majority of chemotherapeutics developed during the last century work by disturbing processes essential for the cell cycle, chiefly DNA synthesis, DNA replication, and chromatid segregation [157]. Medicinal plants are an abundant source of bioactive molecules and represent an attractive alternative to other treatments because several plant-derived compounds have displayed lower toxicity and higher selectivity against cancer cells [158]. Numerous substances in a whole-food plant-based diet have protective and inhibitory effect on tumor growth [159].Common anticancer drugs exhibit lower efficacy against cancer stem cells because of their biological features. Preventing cancer requires the adoption of healthier choices and a moderate amount of exercise.

Modifications in lifestyle such as reducing tobacco smoking rates and encouraging healthier diets as well as cancer screening programs should be a health system priority in order to decrease the mounting problem of cancer-related mortality and morbidity [160]. Glycoprotein modifications are considered as a hallmark of cancer while high expression in body fluids represents an opening for cancer assessment [161]. Nano-medicine application in cancer immunotherapy is currently one of the most exciting areas in cancer therapeutic intervention. Indoleamine-2,3-dioxygenase inhibition in certain diseases may result in noteworthy therapeutic effects. Tumor-targeted chemotherapy is an advanced technique and has more advantages as paralleled to the conventional chemotherapy [162].

Wearable activity displays are increasingly being used to find objective methods of physical activity in oncology trials with additional analysis with artificial aptitude. There is potential for their use to magnify to evaluate and predict clinical outcomes such as survival, quality of life, and treatment acceptance in future studies [163]. Clinical trials have suggested positive relations between flavonoid intake and human health, because the dietary flavonoids have anticancer properties [164]. Flavonoids due to their nontoxicity in nature and enormous, wide ranging aspect of its benefits in biological activities have been intensively studied for their health benefits also added to its plentiful obtainability in our daily diets, for example, green leaves, fruits, vegetables, red wine, and tea [164]. Crocetin a carotenoid compound isolated from the stigma of *Crocus sativus* L. (saffron) has shown encouraging effects as an anti-tumor agent in animal models and cell culture systems. It delays the growth of cancer cells via preventive nucleic acid synthesis, enhancing anti-oxidative system, and inducing apoptosis and differentiation pathways [165]. Rise in cancer immunotherapy, the link among immune cells, inflammation, and cancer is a major effort, and nuclear factor-kappa B (NF-κB) could be an important regulator for the achievement of these remedies [166].

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